# Optimization of guidance response in human embryonic stem cell derived midbrain dopaminergic neurons in development and disease

## Grant Award Details

Optimization of guidance response in human embryonic stem cell derived midbrain dopaminergic neurons in development and disease

**Grant Type:** SEED Grant

**Grant Number:** RS1-00271

**Investigator:**

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| **Name:** | Susan McConnell |
| **Institution:** | Stanford University |
| **Type:** | PI |

**Disease Focus:** Parkinson's Disease, Neurological Disorders

**Human Stem Cell Use:** Embryonic Stem Cell

**Award Value:** $607,363

**Status:** Closed

## Progress Reports

**Reporting Period:** Year 2

**View Report**

## Grant Application Details

**Application Title:** Optimization of guidance response in human embryonic stem cell derived midbrain dopaminergic neurons in development and disease

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| **Public Abstract:** | A promising approach to alleviating the symptoms of Parkinson's disease is to transplant healthy dopaminergic neurons into the brains of these patients. Due to the large number of transplant neurons required for each patient and the difficulty in obtaining these neurons from human tissue, the most viable transplantation strategy will utilize not fetal dopaminergic neurons but dopaminergic neurons derived from human stem cell lines. While transplantation has been promising, it has had limited success, in part due to the ability of the new neurons to find their correct targets in the brain. This incorrect targeting may be due to the lack of appropriate growth and guidance cues as well as to inflammation in the brain that occurs in response to transplantation, or to a combination of the two. Cytokines released upon inflammation can affect the ability of the new neurons to connect, and thus ultimately will affect their biological function. In out laboratory we have had ongoing efforts to determine the which guidance molecules are required for proper targeting of dopaminergic neurons during normal development and we have identified necessary cues. We now plan to extend these studies to determine how these critical guidance cues affect human stem cell derived dopaminergic neurons, the cells that will be used in transplantation. In addition, we will examine how these guidance cues affect both normal and stem cell derived dopaminergic neurons under conditions that are similar to the diseased and transplanted brain, specifically when the brain is inflamed. Ultimately, an understanding of how the environment of the transplanted brain influences the ability of the healthy new neurons to connect to their correct targets will lead to genetic, and/or drug-based strategies for optimizing transplantation therapy. |
| **Statement of Benefit to California:** | The goal of our work is to further optimize our ability to turn undifferentiated human stem cells into differentiated neurons that the brain can use as replacement for neurons damaged by disease. We focus onParkinson's disease, a neurodegenerative disease that afflicts 4-6 million people worldwide in all geographical locations, but which is more common in rural farm communities compared to urban areas (Van Den Eeden et al., 2003), a criteria important for California's large farming population. In Parkinson's patients, a small, well-defined subset of neurons, the midbrain dopaminergic neurons have died, and one therapeutic strategy is to transplant healthy replacement neurons to the patient. Our work will further our understanding of the biology of these neurons in normal animals. This will allow us to refine the process of turning human ES cells onto biologically active dopaminergic neurons that can be used in transplantation therapy. Our work will be of benefit to all Parkinson's patients including afflicted Californians. In addition to the direct benefit in improving PD therapies, discoveries from this work are also likely to generate substantial intellectual property and further boost clinical and biotechnical development efforts in California. |